63-3-1

MEMORANDUM
RM-3544-PR
APRIL 1963

ANALYSIS OF CHEMICAL CONSTITUENTS OF BLOOD BY DIGITAL COMPUTER

James V. Maloney, Jr., M. D., James C. DeHaven,
Edward C. DeLand and Gilbert B. Bradham, M. D.

PREPARED FOR:
UNITED STATES AIR FORCE PROJECT RAND

The RAND Corporation
SANTA MONICA • CALIFORNIA

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This research is sponsored by the United States Air Force under Project RAND—contract No. AF 49(638)-700 monitored by the Directorate of Development Planning, Deputy Chief of Staff, Research and Development, Hq USAF. Views or conclusions contained in this Memorandum should not be interpreted as representing the official opinion or policy of the United States Air Force.

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PREFACE

This Memorandum reports the results of a blind competition between experiments performed with a mathematical model of the human respiratory subsystem using an electronic computer, and by a team of physicians and chemists working in a surgical laboratory on the same biochemical problems. The principal purpose of this exercise was to determine if the model is adequate to forecast accurately the changes that will occur in this subsystem when it is subjected to various forms of stress. The results of this competition were gratifying in that the model gave an excellent performance in every test, indicating that even in its present state of development it can find a useful place in physiologic research. For the Air Force, we anticipate its possible use in helping to explore physiologic response to stressful environments and in determining viable limits without endangering human life. Other uses in medicine are suggested in the text.

This research is part of a continuing Project RAND study of the use of a mathematical procedure for developing models to represent the functions of human physiological subsystems. In this Memorandum, we have attempted to describe the model and its applications in a way that will be understandable to those who are not specialists in either biophysical chemistry or mathematical programming.

For those who are, references to technical descriptions of the model can be found at the end of the Memorandum. A condensation of this material was presented by James V. Maloney, M.D., at the twenty-fourth annual meeting of The Society of University Surgeons, Seattle, Washington, on February 8, 1963.

Of the four authors, James V. Maloney, M.D., and Gilbert B. Bradham, M.D., are Associate Professor of Surgery and NIH Fellow, respectively, at the School of Medicine, Department of Surgery, University of California Medical Center at Los Angeles. Their participation in this study, including the laboratory investigations, was supported by United States Public Health Service grants-in-aid (H-2812 and HTS-5357).

SUMMARY

Recent advances in mathematical programming techniques for complex biochemical systems have made it feasible to construct a computer simulation of the biochemical behavior of human blood. Changes in concentration of some 56 different constituents of plasma, erythrocytes, and alveolar gas can be determined by the model when it is subjected to various simulated stresses. Within two minutes, the digital computer, following programmed instructions describing the basic chemical and thermodynamic reactions of the blood, prints in tabular form the alterations in blood chemistry. A blind competition between the computer and a team of physicians and chemists in a surgical laboratory, working on the same biochemical problem, has been carried out. Alterations in blood chemistry occurring with addition alkalosis, hypothermia, respiratory acid-base problems, saline infusion, hyperbaric oxygenation, and metabolic acidosis have been studied. Over 1,000 laboratory analyses have been compared with computer predictions. In no instance has the computer model been proved in error.

It has thus become possible for the surgeon to perform with extreme rapidity complex biochemical experiments without employing animals, patients, or laboratory analyses. Although the digital equipment is expensive ($2,000,000), the cost of a complete blood study is only $10.00.

Additional advantages are the saving of time and energy, the avoidance of laboratory error, and the possibility of exploring biochemical frontiers for which no satisfactory method of laboratory analysis exists.

The application of modern, high-speed, digital-computer techniques to medicine opens a whole new era of clinical research and treatment.

CONTENTS

THE ANALYSIS OF CHEMICAL CONSTITUENTS OF BLOOD BY DIGITAL COMPUTER*

James V. Maloney, Jr., M.D., James C. DeHaven, Edward C. DeLand, and Gilbert B. Bradham, M.D.
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1. INTRODUCTION

The sum of medical knowledge has become so vast that a single human mind can no longer encompass all of the interwoven complexities of the human system at any one time. To deal with this complexity, the physician has resorted to specialization, but even the specialties have now become very abstruse. The physical scientist, when faced with analogous difficulties, has availed himself of the high-speed computer. Computers have proved particularly helpful in the handling of complicated systems of many inter-related variables; yet, despite the availability of computer science for the past 10 to 15 years, there has been little application of digital computer technology to the analysis of complex biochemical systems [13].

To the practicing surgeon, most of the discussion regarding computers in medicine has been either too technical to be easily understood or too oversimplified to be informative. The present paper, in which the

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authors describe an application of a digital computer to the analysis of the chemical constituents of blood, is directed toward bridging the communication gap which exists between the physician and the computer scientist.

The most likely uses for computers in the field of medicine may be listed as follows:

1. Data sorting - as is done commonly in hospital record rooms.
2. Data retrieval - such as the automatic calculation of telephone bills.
3. Computation - an example of which is the chi square determination in medical statistics.
4. Simulation - for example, the mathematical representation of a biological system in which there is a flow of ions and water from one compartment to another.

There has been much discussion recently concerning the application of computers to medicine, particularly in relation to medical diagnosis by data sorting and probability-correlation techniques. However, the more sophisticated problem of simulation of complex biological systems, which is described here, may well offer the most promising application of computers to medical science.

Until a few years ago, the principal bottleneck in the application of high-speed electronic computers to biological systems was the lack of appropriate mathematical methods.

Then in 1959 two of the present authors (DeHaven and DeLand), along with Dantzig and associates [7], showed how nonlinear programming methods for representing chemical phenomena can be applied to biological systems. These mathematical methods have recently been used to construct a model of the human external respiratory system [8]. The present paper describes the application of this technique to the analysis of the intracellular and extracellular constituents of the blood, as they are of interest to the surgeon.

Although an analysis has been made of the chemical states of blood both with an analog [9] and a digital computer, the present report will be confined to results with the digital apparatus. Despite the relatively long solution time of the digital computer (55 seconds), its inherent accuracy (better than 1 per cent) makes it preferable at the present time to the speedier, but less precise, analog computer.

2. THE MATHEMATICAL MODEL

The first step in the simulation procedure was to describe mathematically all of the major biochemical reactions of the blood by means of a set of equations that could be solved simultaneously for the concentrations of blood constituents at a steady-state equilibrium. For the purpose of illustration, consider the reaction of carbon dioxide with water:

$$(1) \qquad CO_2 + H_2O \overset{K_1}{\rightleftharpoons} H_2CO_3 \overset{K_2}{\rightleftharpoons} H^+ + HCO_3^- \overset{K_3}{\rightleftharpoons} H^+ + CO_3^{=}.$$

The mass-action concept states that if additional CO_2 is added to the above reaction, the equilibrium shifts to the right; if additional carbonate is added, the equilibrium moves to the left.

A second example might be the reaction of sodium chloride and lactic acid in water solution:

$$(2) \qquad NaCl + HLac \rightleftharpoons NaLac + HCl \rightleftharpoons Na^+ + Lac^- + H^+ + Cl^-.$$

These chemical constituents will interact until the resultant concentrations of each of the eight chemical species represented are such that the free energy of the whole system is at a minimum, in keeping with the precepts of thermodynamics. Since the free energy of formation of these compounds is known, it is possible to calculate with paper and pencil the amount of each of the compounds formed, provided one knows the number of moles of material put into the system. A convenient method of expressing the various chemical combinations that appear in the foregoing example is shown in Table I. The array of entries in this table is referred to as a "matrix." On the left are represented the various input elements to the system (a_1 - a_4). At the top are represented all possible chemical species (x_1 - x_8) formed by the input elements.

TABLE I

MATRIX FOR REACTION OF NaCl AND HLac

INPUTS	OUTPUTS							
	X_1 NaCl	X_2 NaLac	X_3 HCl	X_4 HLac	X_5 Na^+	X_6 Cl^-	X_7 H^+	X_8 Lac^-
a_1 - Na^+	1	1	0	0	1	0	0	0
a_2 - Cl^-	1	0	1	0	0	1	0	0
a_3 - H^+	0	0	1	1	0	0	1	0
a_4 - Lac^-	0	1	0	1	0	0	0	1

The vertical columns indicate the input elements required to form a given output species. Such a matrix is a form commonly used for the solution of problems by computers.

It is apparent that by combining the constituents of equations (1) and (2) above, a whole new series of dissociation and combination products will be produced. It is also apparent that the hydrogen ion formed by the dissociation of the H_2CO_3 in equation (1) will have a mass-action effect on the dissociation of the lactic acid in equation (2). Since the equations are interdependent, they must be solved simultaneously for the amounts of output products formed.

$$\left.\begin{array}{ll} (1) & CO_2 + H_2O \\ (2) & NaCl + HLac \end{array}\right] \longrightarrow \begin{array}{l} H_2CO_3,\ H^+,\ HCO_3^-,\ OH^-,\ CO_3^{=},\ NaLac, \\ HCl,\ Na^+,\ Cl^-,\ Lac^-,\ Na_2CO_3,\ NaHCO_3,\ NaOH \end{array}$$

There are now so many dissociation constants and free-energy values involved that even with the aid of a desk calculator, it would take several weeks to solve for the concentrations of the various end products. However, by simply adding carbon dioxide and water to the matrix in Table 1, one could quickly obtain the answers with the aid of a high-speed digital computer. Thus, equations may be serially added to such a matrix so as to describe all the major chemical reactions of clinical interest. The solution of

a problem in matrix form represents a typical application of modern computers. This is the essence of the simulator being presented.

A mathematical model may be constructed by writing equations involving all of the major chemical species represented in both the intracellular and extracellular phases of the blood, including plasma protein and hemoglobin. Since gases affect hemoglobin, a complete description of the partial pressures of all gases in the alveoli, as well as a representation of the reactions of hemoglobin, is an essential part of the model. The solution of large systems of equations in matrix form is a simple project for a digital computer. However, it is necessary to place certain limitations (constraints) on the biochemical system if the computations are to take into consideration the fundamental laws of thermodynamics and also to represent accurately the chemical reactions of human blood.

1. Conservation of mass constraint. In accordance with the Law of Conservation of Mass, the mass of compounds formed (computer output) can be no different than the mass of material put in the system (computer input).

2. Charge constraint. A semipermeable membrane divides blood into intracellular and extracellular components. Certain elements (e.g., protein) cannot diffuse through the membrane. Since both of the compartments must be

electrically neutral, there will occur an unequal distribution of diffusable ions (classic Gibbs-Donnan effect). The sodium-pump mechanism of the cell causes further disparate concentration of ions in the two compartments, and this is also represented in the model.

The problem is solved within the limitations imposed by the above constraints by finding that combination of chemical products in the several compartments which permits the total free energy of the system to be at a minimum. The model is thus not one of pure classical equilibrium, but rather reflects the steady-state gradients which are present within the blood.

3. THE MUSE PROGRAM

A large digital computer is required for this project, because of the number of computations required (in the order of 6,000,000). In the early stages of the program, an IBM 704 computer was used, and at the present time an IBM 7090 series computer is employed. Because of the slow access time of the magnetic-tape memory, a large random access memory is essential. The active memory of the IBM 7090 computer consists of 32,000 words, each of which is composed of 32 binary bits of information. For ease of reference, the program is referred to as MUSE (Medical Use of Simulation Electronics). The construction of the program progressed through the following steps:

1. Mathematical formulation. A complete mathematical description of all the major biochemical reactions of the blood was formulated, and the appropriate constraints were described in mathematical terms.

2. Program. A program (i.e., a plan of procedure) was designed which resolved the problem into logical sequential steps and instructed the computer to carry out the desired operations. These instructions were then coded in one of the languages common to computer science (Fortran was employed in this instance) to permit the programmer to communicate with the machine. Two sets of punch cards were prepared: (1) instruction cards, containing the sequential operation instructions for the computer; (2) data input cards describing the biochemical input to the system.

3. Computer. The computer that was used operates on the basis of the binary number system (which employs just two numerals, 0 and 1, with all numbers in the usual base ten being represented by combinations of these two symbols) and Boolean logic (which is illustrated by means of the "flow diagram" in Fig. 1). The computer uses the binary system because the two symbols, 0 and 1, or the two signals "Yes" and "No," can be indicated by an Off and On switch in the computer. An input device converts the decimal numbers to their binary equivalents, and stores all of the information contained on the

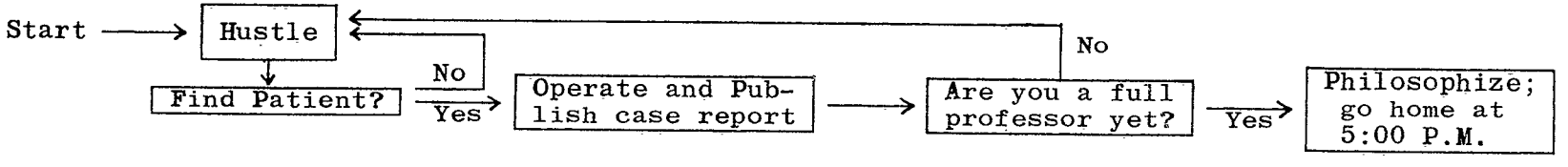

Fig. 1. Program for achieving success in academic surgery

instruction cards and data input cards in the active memory. The entire computer operation is under direction of the control unit, which directs retrieval of information from the memory unit, transfers it to the arithmetic unit, performs the desired instructions, and returns the results to new addresses in the memory unit. An example of such computer instructions, written in English (instead of Fortran), is presented below:

Instruction 411. Take the number of H^+ ion moles stored in Memory Location 220A and place in Arithmetic Unit.

Instruction 412. Take the number of liters of H_2O stored in Location 1520B in Memory Unit and transfer to Arithmetic Unit.

Instruction 413. Divide the amount of H^+ ion by the amount of H_2O.

Instruction 414. Take the negative logarithm of the result and store in memory location 99 as pH.

The computer, following programmed instructions, determines the concentration of each constituent of the blood that will satisfy the equations and constraints imposed upon the system. The problem is solved repetitively until the free energy is at an irreducible minimum. The machine is then instructed by the control unit to stop, and the concentrations of all the blood constituents stored in the memory are fed to the magnetic output tape.

After these amounts have been reconverted from the binary to the decimal number system, the results are printed.

The solution of the problem before printing takes about 55 seconds. This speed is possible because the computer is driven by a 5-megacycle oscillator. It takes from two to fifteen pulses of current, each lasting 1/5,000,000 second, to perform one step of the program. About 6,000,000 computations, each consisting of many steps, are required. The output on magnetic tape is then recorded by automatic printer in alphanumeric language (a combination of English alphabet and Arabic numerals). Print-out time varies from 20 seconds (at 72,000 characters per minute) to 7 minutes, depending on the capacity of the printer. The concentration of the ions in each compartment of the system is specifically identified. A typical print-out page, together with its matrix, is illustrated in Fig. 2. On the top half of the page are the values in moles and mole fractions for the 56 output species in the various compartments (alveolar gas, plasma, intracellular). The matrix and some of the physical constants employed are at the lower half.

As a first test of the computer model, the machine was given as inputs the number of moles of oxygen, chloride, sodium, etc., which make up a liter of blood and was directed to distribute them into the proper compartments in appropriate concentrations. As is seen in Table 2,

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REPORT STD PLUS CA.MG   TWO  DEC 62                                          PAGE 1
   12 ITERATIONS

     AIR CUT          XBAR =  99.8994694     XBAR ADJUSTED =  99.8994856
MOLES
 O2    = 1.3148E 01   CO2   = 5.2603E 00   N2    = 7.5400E 01   H2O   = 6.0913E 00
MOLE FRACTIONS
 O2    = 1.3161E-01   CO2   = 5.2656E-02   N2    = 7.5476E-01   H2O   = 6.0974E-02

     PLASMA           XBAR =  35.3711915     XBAR ADJUSTED =  35.3712201
MOLES
 O2    = 8.2559E-05   CO2   = 8.5187E-04   N2    = 2.6509E-04   H+    = 2.7098E-08   OH-   = 3.5836E-07   CL-   = 1.0043E-01
 NA+   = 1.2C6OE-01   K+    = 3.3690E-03   H2O   = 3.5114E 01   HCO3- = 1.6152E-02   H2CO3 = 1.2094E-06   CO3=  = 2.1531E-05
 EXTRA = 0.           MISCPL= 1.1553E-02   CA++  = 2.9841E-03   MG++  = 1.2242E-03
MOLE FRACTIONS
 O2    = 2.3341E-06   CO2   = 2.4084E-05   N2    = 7.4944E-06   H+    = 7.6611E-10   OH-   = 1.0131E-08   CL-   = 2.8392E-03
 NA+   = 3.4095E-03   K+    = 9.5247E-05   H2O   = 9.9272E-01   HCO3- = 4.5665E-04   H2CO3 = 3.4192E-08   CO3=  = 6.0872E-07
 EXTRA = 0.           MISCPL= 3.2662E-04   CA++  = 8.4364E-05   MG++  = 3.4610E-05

   RED CELLS          XBAR =  14.4789006     XBAR ADJUSTED =  14.4789522
MOLES
 O2    = 5.5164E-05   CO2   = 3.4870E-04   N2    = 1.7890E-04   H+    = 1.8826E-08   OH-   = 8.6434E-08   CL-   = 2.4222E-02
 NA+   = 8.8218E-03   K+    = 4.1653E-02   H2O   = 1.4373E 01   HCO3- = 4.4812E-03   H2CO3 = 4.9506E-07   CO3=  = 3.5197E-06
 EXTRA = 0.           MISCRC= 2.1129E-02   EXTRA = 0.           EXTRA = 0.           HB4-  = 9.6978E-06   HB4O2 = 3.8415E-05
 HB4O4 = 6.0843E-05   HB4O6 = 5.7705E-05   HB4O8 = 2.1055E-03   CA++  = 2.8595E-04   MG++  = 2.0058E-03   EXTRA = 0.
MOLE FRACTIONS
 O2    = 3.8099E-06   CO2   = 2.4084E-05   N2    = 1.2356E-05   H+    = 1.3002E-09   OH-   = 5.9696E-09   CL-   = 1.6729E-03
 NA+   = 6.0929E-04   K+    = 2.8768E-03   H2O   = 9.9272E-01   HCO3- = 3.0950E-04   H2CO3 = 3.4192E-08   CO3=  = 2.4309E-07
 EXTRA = 0.           MISCRC= 1.4593E-03   EXTRA = 0.           EXTRA = 0.           HB4-  = 6.6979E-07   HB4O2 = 2.6532E-06
 HB4O4 = 4.2022E-06   HB4O6 = 3.9854E-06   HB4O8 = 1.4542E-04   CA++  = 1.9749E-05   MG++  = 1.3853E-04   EXTRA = 0.

REDHEME FICN          XBAR =   0.0003334     XBAR ADJUSTED =   0.0003334
MOLES
 *H2HB = 1.9114E-04   *HHB  = 2.3736E-04   -HB   = 9.4157E-05
MOLE FRACTIONS
 *H2HB = 5.7327E-01   *HHB  = 7.1180E-01   -HB   = 2.8240E-01

OXYHEME FICN          XBAR =   0.0087550     XBAR ADJUSTED =   0.0087550
MOLES
 *H2HBO= 3.5345E-05   *HHBO2= 1.3884E-03   -HBO2= 7.3313E-03
MOLE FRACTIONS
 *H2HBO= 4.0372E-03   *HHBO2= 1.5858E-01   -HBO2= 8.3738E-01

RED CARB              XBAR =   0.0003766     XBAR ADJUSTED =   0.0003788
MOLES
 HB-   = 3.3869E-04   HBCO2-= 0.           -HBCO2= 4.0159E-05
MOLE FRACTIONS
 HB-   = 8.9927E-01   HBCO2-= 0.           -HBCO2= 1.0663E-01

OXY CARB              XBAR =   0.0293252     XBAR ADJUSTED =   0.0293246
MOLES
 HBO2- = 2.8C26E-02   HBOCO2= 0.           -HOCO2= 1.2981E-03
MOLE FRACTIONS
 HBO2- = 9.5571E-01   HBOCO2= 0.           -HOCO2= 4.4265E-02
```

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REPORT STD PLUS CA.MG   TWO  DEC 62                                          PAGE 2

INPUTS

M =18  N=56  NC. OF P. = 7  N 1= 4  N 2=16  N 3=24  N 4= 3  N 5= 3  N 6= 3  N 7= 3  N

A(I,J) MATRIX
    1 2 3 4 5 6 7 8 9101112131415161718192021222324252627282930313233343536373839404142434445464748495051525354555 6
 1  1 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 2 3 4 0 0 0 0 0 0 0 0 0 0 0 0 0 0
 2  0 1 0 0 0 1 0 0 0 0 0 0 0 1 1 1 0 0 0 0 0 1 0 0 0 0 0 0 0 1 1 1 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 0 0 1
 3  0 0 1 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
 4  0 0 0 1 0 0 0 1 0 0 0 C 1 0 1-1 0 0 0 0 0 0 0 1 0 0 0 0 1 0 1-1 0 0 0 0 0 0 0 0 0 0 0 1 0-1 1 0-1 0 0-1 0 0-1
 5  0 0 0 0 1 0 0 0 0 1 0 0 0 1 1 1 1 0 0 0 0 0 0 0 1 0 0 0 0 1 1 1 1 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
 6  0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
 7  0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
 8  0 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
 9  0 0 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
10  0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
11  0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
12  0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 1 1 1 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
13  0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
14  0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
15  0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
16  0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
17  0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
18  0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0

B(I)
  1.315683E 01   5.283490E 00   7.540044E 01   5.556950E 01   5.559900E 01   1.246500E-01   1.294200E-01   4.506000E-02
  1.155000E-02   2.112750E-02   2.272500E-03   0.             0.             0.             0.             0.
  3.270000E-03   3.230000E-03

FREE ENERGY CONSTANTS
  0.            -7.690000E 00  -1.152000E 01  -3.660000E 01   1.094000E 01   0.             0.             0.
  0.             0.             0.             2.879000E 00  -3.939000E 01  -2.135000E 01  -3.284000E 01   6.260000E 00
  0.             0.             0.             8.580000E-01   1.045000E 01   0.            -5.000000E-01   0.
  0.             0.             2.251000E 00   0.            -3.939000E 01  -2.149000E 01  -3.284000E 01   6.120000E 00
  0.             0.             0.             0.             0.            -1.902800E 00  -2.888900E 00  -3.362200E 00
 -7.485400E 00   1.981C00E 00   0.             0.            -1.563900E 01   0.             2.181000E 01  -1.679000E 01
  0.             1.897790E 01   0.             0.             1.195900E 01   0.             0.             1.289900E 01

INITIAL GUESSES
  6.000000E-01   2.000000E-01   3.000000E 00   3.000000E-01   6.750000E-05   7.000000E-04   2.170000E-04   2.100000E-08
  3.050000E-07   5.850000E-02   8.050000E-02   4.000000E-03   2.895000E 01   1.350000E-02   9.920000E-07   1.850000E-05
  0.             8.800000E-03  10.000000E-04  10.000000E-05   6.870000E-05   4.340000E-04   2.220000E+04   2.090000E-08
  1.180000E-07   2.290000E-02   4.600000E-03   5.000000E-02   1.795000E 01   6.130000E-03   6.170000E-07   5.280000E-06
  0.             1.870000E-02   0.             0.             1.200000E-08   1.000000E-07   5.800000E-06   6.400000E-05
  2.230000E-03  10.000000E-05  10.000000E-04   0.             4.700000E-05   2.400000E-03   3.600000E-03   2.000000E-03
  4.500000E-03   2.500000E-03  10.000000E-03   0.            10.000000E-03   7.700000E-01   0.            10.000000E-02

CONTROL NUMBERS
 -0.            10.000000E-03   0.             9.000000E-01   9.900000E-01

 MISCELLANEOUS DAT
  1.000000E 00   5.519000E 01   7.370664E 00   7.140938E 00   0.             0.             0.             0.
  0.             0.
```

Fig. 2. Computer print-out for addition of saline to the blood system.

TABLE 2

COMPARISON OF COMPUTER OUTPUTS WITH STANDARD BIOLOGICAL DATA

INPUTS	Computer (Moles/Vol Produced)	Handbook of Biological Data (Moles/Vol Existing)
	Alveolar Gas	
O_2	0.1314	0.1315
CO_2	0.0526	0.0526
N_2	0.754	0.754
H_2O	0.0610	0.0611
	Plasma	
O_2	6.65×10^{-5}	6.34×10^{-5}
CO_2	6.87×10^{-5}	6.96×10^{-4}
N_2	2.13×10^{-4}	2.16×10^{-8}
H^+	2.06×10^{-8}	2.10×10^{-7}
OH^-	3.07×10^{-7}	3.57×10^{-2}
Cl^-	5.70×10^{-2}	5.70×10^{-2}
Na^+	7.64×10^{-2}	7.64×10^{-3}
K^+	2.31×10^{-3}	2.31×10^{-2}
H_2O	2.83×10^{-2}	2.87×10^{-2}
HCO_3^-	1.38×10^{-7}	1.37×10^{-2}
H_2CO_3	9.77×10^{-5}	Not reported
$CO_3^=$	1.95×10^{-3}	Not reported
Ca^{++}	2.85×10^{-3}	2.86×10^{-3}
Mg^{++}	9.35×10^{-4}	9.35×10^{-4}
	Red Cells	
O_2	7.03×10^{-5}	6.43×10^{-5}
CO_2	4.44×10^{-4}	4.73×10^{-4}
N_2	2.28×10^{-4}	2.20×10^{-8}
H^+	2.14×10^{-8}	2.09×10^{-7}
OH^-	1.23×10^{-7}	1.41×10^{-2}
Cl^-	2.29×10^{-2}	2.40×10^{-3}
Na^+	8.36×10^{-3}	8.37×10^{-2}
K^+	4.27×10^{-2}	4.27×10^{-2}
H_2O	1.83×10^{-2}	1.80×10^{-3}
HCO_3^-	6.40×10^{-3}	5.98×10^{-3}
H_2CO_3	6.32×10^{-7}	Not reported
$CO_3^=$	5.63×10^{-6}	Not reported
Ca^{++}	4.10×10^{-4}	4.5×10^{-4}
Mg^{++}	2.29×10^{-3}	2.29×10^{-3}

Mean % difference = - 0.84
S. E. = ± 0.94

the predicted computer values agreed with those given in the Handbook of Biological Data within -0.84 mean per cent difference, S.E. $\pm$ 0.94. The information in the Handbook of Biological Data represents the mean values of many determinations, and thereby averages out random laboratory error. Since the computer gives the same value as the mean obtained by laboratory experiment, the computer has greater precision than any particular laboratory determination used in calculating the mean values given in the Handbook.

4. APPLICATIONS

The previous example demonstrated the ability of the model to simulate with a high degree of accuracy a complex biochemical system in normal man. The cogent question was whether the model would function accurately when stressed by pathological conditions, for if so, medicine would have available a tool of tremendous clinical import. In order to obtain an unbiased evaluation of the usefulness of the simulator under conditions of stress, a blind competition was carried out between the laboratory and the MUSE program. The problems selected for the test were ones which are of current surgical interest and to which computer techniques appeared applicable (e.g., acid-base balance, hypothermia, clinical respiratory problems, validation of published literature, and hyperbaric oxygenation).

Acid-base balance. Addition alkalosis, a rare condition which may follow treatment of peptic ulcer with alkali, is a sufficiently bizarre acid-base derangement to present a real challenge to the flexibility of the computer model. Most clinicians recognize that in this condition pH is increased; however, it is not generally recognized that such an elevation of pH involves the simultaneous change in concentration of every other ion, both in the plasma and within the interior of the red cell. For the laboratory analysis, blood samples were removed from 10 normal volunteers, and alkalosis was produced in the samples by the addition of 44.6 milliequivalents of sodium bicarbonate to a liter of blood. The pCO_2 and pO_2 were maintained constant, and the reactions were allowed to proceed to completion at 37°C. Table 3 compares the predictions obtained by MUSE with the average results obtained by laboratory analysis over a period of several weeks. While the results by the two methods agree closely, the sodium heparin used to anticoagulate blood in the laboratory experiments results in an apparent elevation of serum-sodium values above predicted levels. This increased serum sodium would indirectly and unavoidably affect all other ions. It is pertinent that the computer predicts actual hydrogen-ion concentration; the laboratory value for hydrogen-ion concentration is obtained from pH measurement by glass electrode. Since the standard pH

TABLE 3

COMPARISON OF LABORATORY RESULTS WITH MUSE PREDICTIONS
FOR BLOOD CHANGES IN ADDITION ALKALOSIS

BLOOD CONSTITUENTS	Before Na HCO_3	After Na HCO_3	
	Normal Values	Lab. (10 Experiments)	Computer
Hct	45 vol %	37.2	36.9
Plasma Na^+	139 mEq/L	188	178
Plasma K^+	4.2 mEq/L	4.5	4.52
Plasma Cl^-	103 mEq/L	102.7	97.5
Plasma H^+	3.8×10^{-8} M/L	1.58×10^{-8}	1.24×10^{-8}
Osmolality	290 mOsm/L	370	380

method measures hydrogen-ion activity rather than hydrogen-ion concentration, there is probably some error in the laboratory result. By studying many blood samples, laboratory errors were averaged out so that the laboratory method approached the accuracy of the computer. For those blood constituents which were demonstrated by the computer to change only slightly with addition alkalosis (e.g., potassium), literally hundreds of laboratory experiments would be required in order to obtain statistically significant data to show the small changes which are predicted by the computer.

Hypothermia. An example of the clinical problem-solving capacity of the model is its application to the solution of the polemic regarding the acid-base status of blood during profound hypothermia[2]. This controversy concerns the interpretation of laboratory measurement of pH and its influence on the oxyhemoglobin dissociation during hypothermia. Inasmuch as MUSE may be programed to describe the reactions of blood not only at 37°C, but at any temperature desired, it can be used to investigate various aspects of this problem. The details of this analysis will be described elsewhere[4]. Suffice it to say that oxyhemoglobin dissociation curves may be obtained at any specific temperature, at any pH, at any hematocrit, or at any gas pressure or ion concentration.

Figure 3 shows the close agreement between oxygen

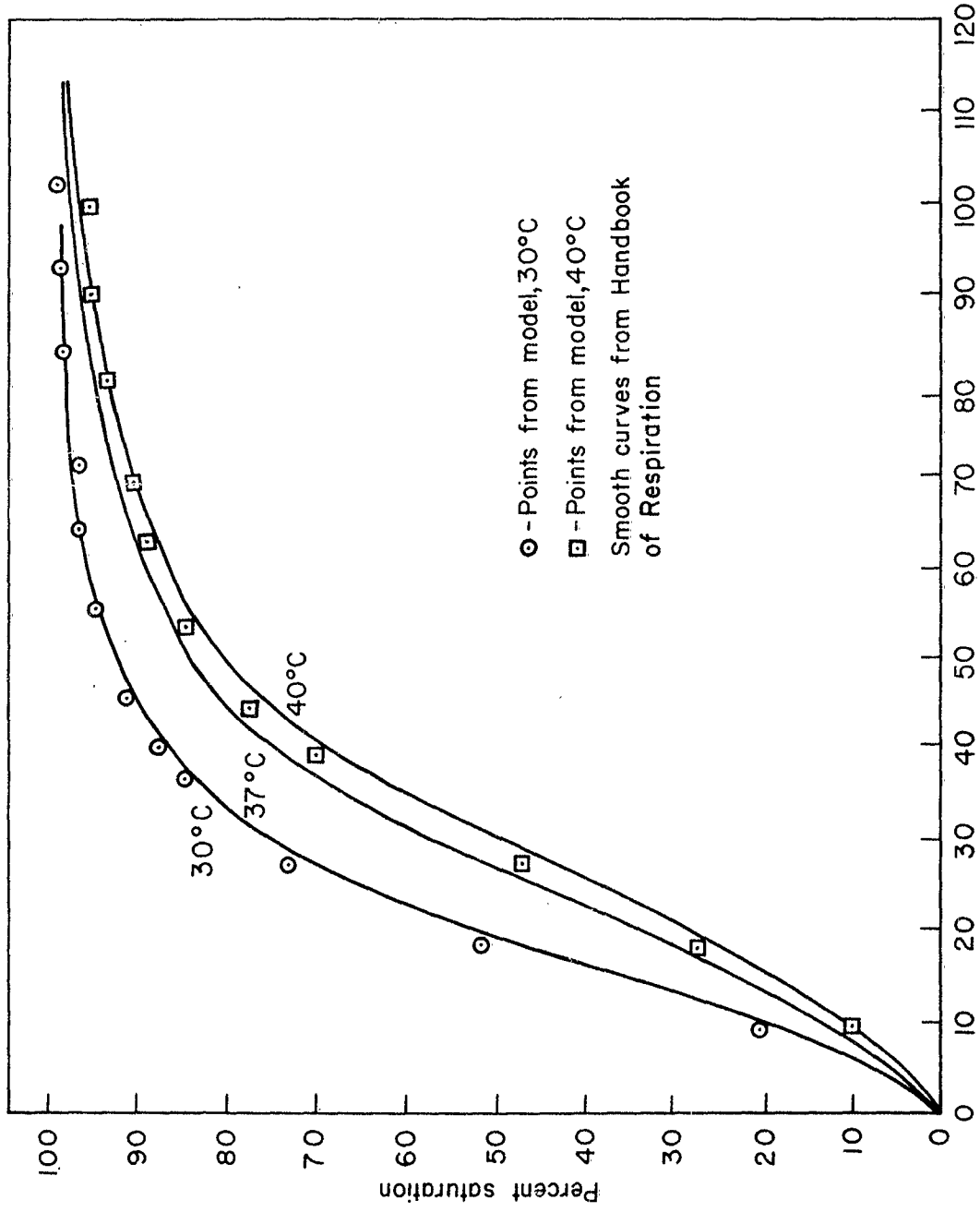

Fig. 3 — Comparison of oxygen dissociation curves obtained from computer model and from handbook

dissociation curves (for blood at pH 7.4 and at three different temperatures) obtained by the model and those presented in the "Handbook of Respiration." The computer will describe oxyhemoglobin dissociation curves for any possible combination of temperature and pH (or, for that matter, for any combination of other blood conditions).

Not only is the over-all oxygen saturation described, but the computer indicates the saturation of each of the four molecular types of hemoglobin first postulated by Adair[1]. The above mentioned polemic can, therefore, be resolved in 55 seconds of computer time, at a cost of $10.00, as compared to the tens of thousands of dollars of United States Public Health Service money spent by the authors and by others in attempts to answer this problem[12].

Clinical respiratory problems. Since the computer can be made to "breathe" any mixture of oxygen, carbon dioxide, and nitrogen merely by changing its inputs, it serves as a magnificent tool with which to study respiratory acidosis or alkalosis. The clinician is able to obtain not only a grasp of the respiratory factors (pCO_2, pH, shift of dissociation curve, etc.), but also a detailed evaluation of the changes in the intra- and extracellular chemistry brought about by the abnormal respiratory conditions.

Research application. Visualization of an entire system, rather than only its component parts, gives insight

into function of the system. It is, therefore, natural that the MUSE program should bring to light heretofore unrecognized facts. As an example of this, it was noted in the early experiments that the computer when "infused" with saline would lower the pH of both plasma and the interior of the red cells. A cause for this observation was sought. Review of the computer output, which included a complete analysis of the alveolar gas phase as well as of plasma and the interior of the erythrocytes, was made. It was noted that when saline solution was added to the "venous blood" of the model, carbon dioxide disappeared from the lungs and appeared in the blood. The injected saline was obviously taking up carbon dioxide from the lungs as it equilibrated to the pCO_2 of alveolar gas. The additional hydrogen ions resulting from the dissociation of carbonic acid were clearly responsible for the acidosis observed.

A single confirmatory experiment was performed. An anesthetized dog was connected to a spirometer. Ten milliliters per kilogram of body weight of neutral physiologic saline were infused intravenously. The shift in an acid direction on the Astrup nomogram[3] is illustrated in Fig. 4. The spirometer tracing showed the sudden absorption of carbon dioxide by the blood from the alveolar gas. Three points are important in this example: (1) the original observation of acidosis produced by

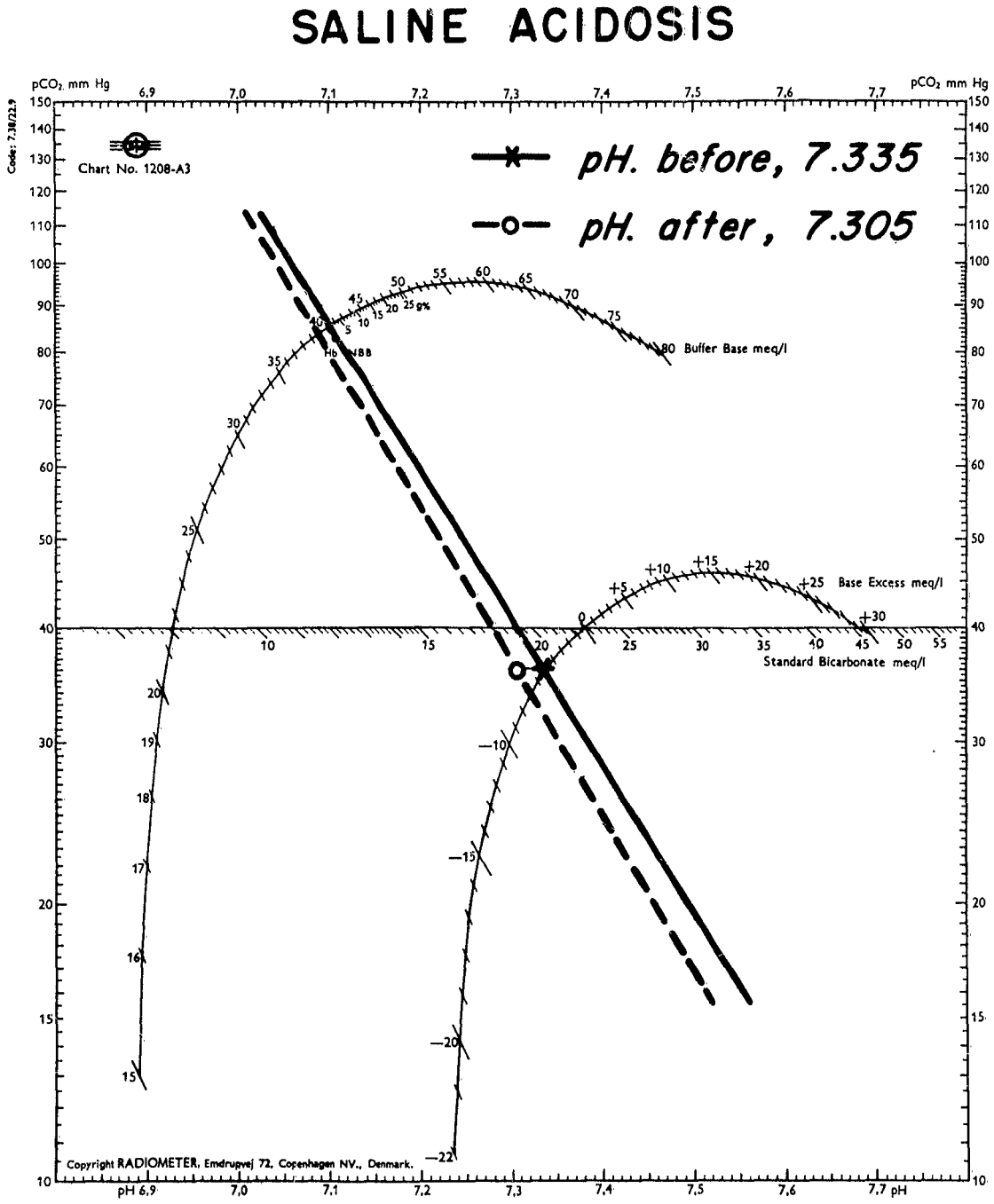

Fig. 4. Astrup nomogram showing saline acidosis in a dog.

saline, overlooked by generations of physicians, was made by the computer. The acidosis being slight in degree, is of physiologic rather than clinical importance; (2) the explanation of the mechanism of the new observation was completely contained in the computer output; and (3) only a single animal experiment was required to confirm existence of the syndrome of saline acidosis.

Hyperbaric oxygenation is an example of an area for application of the computer model to current surgical research problems. MUSE will determine the direct effect of hyperbaric oxygenation upon blood-gas contents and blood chemistry. The release of H^+ ions from the hemoglobin molecule, and the subsequent alterations in erythrocyte pH, as well as the alteration in the distribution of other ions, is fully displayed by the computer print-out.

Hematocrit is generally thought by the clinician to be a measure of anemia, rather than as an osmometer reflecting shifts of body fluid. The computer, since it accurately measures other causes of fluid shifts, portrays alterations in hematocrits which occur with changes in blood chemistry. It can, therefore, easily be seen that the erythrocytes serve as a representative osmometer, indicating whole-body intracellular and extracellular shifts of water.

Pedagogy. Since the computer displays a complete

picture of blood chemistry, it may serve as an excellent teaching tool for medical students. An analog computer is currently being employed with the MUSE program for this purpose at U.C.L.A. The practically instantaneous solution time of the analog machine permits the operator to change the concentration of any blood element and immediately observe its effect on all other major constituents of the blood.

Validation of literature. In view of the speed and facility of study by the computer model, it is possible to check the accuracy of data published in the literature with a minimum of effort. In addition to validating published experiments, the computer is capable of greatly expanding biochemical data. Provided that adequate input data is supplied, the MUSE will not only check the accuracy of reported results but will also supply information on blood factors not included in the original report.

In a recent publication on the rheology of blood in hypothermia, Eiseman and Spencer[10] reviewed the evidence for the shift of fluid and electrolytes to the intracellular space during hypothermia. When the computer model is "cooled" to 30°C, the fluid and ion shifts cannot only be seen but are accurately quantitated. This represents another example of the way in which laboratory data of others, as well as hypotheses and speculations, can be critically examined and checked within a few minutes.

Accuracy of MUSE. It is inconceivable that, with existing limitations in our knowledge of body chemistry, the program described here can give a complete and totally accurate picture of a biochemical system. The computer model can be no more accurate or precise than the biological knowledge on which it is based and the skill with which it is programmed. The program can be expanded as new knowledge becomes available. The computation procedure itself can be practically absolved from the possibility of error (except for numerical techniques such as round-off).

Discrepancies between predictions of the model and biological experiments have been diligently sought (albeit unsuccessfully). This search has great potential, particularly in pathological conditions. Should such a discrepancy be found, it would suggest one of two possibilities: (1) since the computer program contains all the pertinent, current biochemical knowledge, some facet of such knowledge must be in error under the pathological condition being studied, or (2) some new and important piece of basic information has been discovered about a disease state.

Over 1,000 laboratory analyses have been compared with computer predictions. Although numerous discrepancies

have been encountered, in no instance has the computer-model been proved at fault. On one occasion, human oversight resulted in the nitrogen being left out of the computer's alveolar gas on a day when the animal in the laboratory was breathing room air. The computer immediately detected the error in input information. Scores of discrepancies between the laboratory and MUSE predictions have been encountered, but in almost all instances it has been possible to attribute the error to the laboratory. The reliability of the computer model led to the identification of a partially occluded flame photometer jet. It permitted detection of a faulty centrifuge when predicted hematocrit changes did not agree with observed values. It identified a pair of blood samples on which the labels had been switched. On one occasion, an analysis of blood from a normal individual was used as input to the computer. After several hundred thousand computations, the machine stopped working and indicated an inconsistency in the inputs, i.e., that it was thermodynamically impossible to have living blood of the composition indicated. After many days of effort, sodium in the heparin used as an anticoagulant was found to be the source of error. When this was corrected, the MUSE program again produced satisfactory results.

5. DISCUSSION

In a previous era, a clinician who was given the figures for pCO_2, CO_2 content, and pH of his patient's serum viewed these measurements as isolated observations. Henderson and Hasselbalch[11] made a significant contribution by correlating these three plasma measurements, so that the clinician has since had a clear understanding of the effect of metabolic and respiratory factors in the acid-base balance of his patient. The computer model described here performs the same function for 53 other known clinically important constituents of the blood.

It might seem surprising, at first, that the computer program could accurately describe the biochemical changes in individuals of the human species, who are known to vary so much from one another. Even though individuals may vary, the same thermodynamic laws govern chemical behavior in all individuals. The computer model is a "standard man," whose biochemical make-up is the average for a large population. When the standard man is subjected to a stress, the result predicted by the computer is that which would be achieved by subjecting a wide range of clinically normal individuals to the same stress. Some individuals vary significantly (e.g., in hematocrit or serum sodium) from the "standard man." Prediction of such a person's response to a specific stress by the standard-man computer model would result in a deviation

in the prediction parallel to the individual's deviation from the standard man. To obtain an accurate answer in the analysis of such an individual's response to a stress, it is only necessary to program into the computer that specific individual's variations from the norm of the population.

It is well recognized that enzyme activities and metabolic pathways may differ in different individuals under different circumstances. However, this observation is not pertinent to the validity of the current model, since in the description of thermodynamic equilibria, it is not necessary to know the specific mechanism of a reaction. For example, although the body uses carbonic anhydrase as a catalyst for carbon-dioxide reactions, this enzyme is not represented in the model, because the carbon-dioxide reactions do proceed, in time, to a steady-state equilibrium without this catalyst. The actual rate of reaction is not of concern to the computer, since it does not operate in real time.

The computer solves problems for steady-state equilibria, without regard to changes in chemistry occurring in time (e.g., such as might occur with the slow renal excretion of electrolytes). In comparing the computer with the laboratory experiments, it is necessary to sample the biological system before such compensatory mechanisms affect it.

The development of this computer program represents an excellent example of interdisciplinary communication. Absence of such communication has resulted in a delay in the application of digital computer methods to medicine, a field in which they may well have one of their greatest applications. It is recognized that the physician cannot overnight become an accomplished mathematician nor the mathematician become a clinician, nor is it necessary for either to do so, provided there is close cooperation among the mathematician, physical chemist, physiologist, and clinician. As pointed out recently by Brown[6], such cooperation can be expected to benefit greatly each of the fields concerned.

The techniques described here may be used to represent other human subsystems, such as the total metabolic system (including digestion, nutrition, and excretory functions); functions of the liver; blood hematopoietic system; hormonal regulatory system; and the central and peripheral nervous system. MUSE should prove valuable in the study areas of body chemistry (e.g., intracellular) for which few methods of laboratory analysis currently exist. Preliminary consideration suggests that the model may be useful in determining limits of viability of the human organism under abnormal environments, such as prolonged periods of space travel.

Although we expect the greatest benefits from this

approach to be in the area of investigation and elucidation of basic body processes, the model can be expected to have practical clinical applications. A previous study by one of the authors (Bradham)[5] has demonstrated the impossibility of making any significant correlation between the usual laboratory determinations of serum sodium, chloride, potassium, and bicarbonate in the hospitalized patient. However, when similar measurements are introduced into the present computer program, a complete survey of blood chemistry is immediately available.

The IBM 7090 digital computer used for the MUSE program has a high initial cost ($2,000,000), which results in a significant hourly charge for computer time ($500). However, a complete blood analysis can be performed by the computer for only $10.00, because of the speed of the machine's operation. This is an insignificant amount when weighed against the cost of determining serum chloride, sodium, potassium, and carbon dioxide combining power by conventional methods.

The lack of computer facilities will not prevent hospitals and medical centers from using the techniques described. At the present time, data transmission systems are available through standard telephone services which permit intercommunication between machines. A trans-continental phone call would allow the data on all patients in the hospital to be transferred to a digital computer

center where it can be analyzed in a few minutes. On completion of the digital analysis, the data can be returned to the hospital by the same method of transmission and recorded directly on paper. Because the machines communicate at superphonic speed in machine language, a brief telephone call permits the transmission of enormous quantities of data.

An example of this long-distance application of computer facilities is the use on a daily basis of the IBM 7090 computer on the U.C.L.A. campus by the Air Force Academy in Colorado Springs and by seven other western universities. Because this computer is now operating three eight-hour shifts a day, a second computer (IBM 7094, the fastest and largest currently available) is being installed at the U.C.L.A. Medical Center exclusively for medical use.

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